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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/518,081	SHAPIRO, LELAND	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-20,23-25,29 and 30* is/are pending in the application.

4a) Of the above claim(s) *5,6,8,9 and 23-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,10,12-20,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

1. In response to the previous Office action on the merits, a Final rejection (Paper No. 16 mailed February 11, 2002), Applicant's filed an after-final amendment and response on January 29, 2003 (Paper No. 15) and an RCE received June 27, 2003 (Paper No. 18) for entry of said after-final amendment. Said amendment cancelled Claims 21-22 and 26-28, amended Claims 1, 3, 4, 8, 9, 12, 14, 16, 18, 19, and 23-25, and added new Claims 29-30. Thus, Claims 1-10, 12-20, 23-25, and 29-30 are pending.

Election

2. As previously noted, Applicants elected methods of treatment using α_1-antitrypsin, the elected species of serine protease inhibitor. As amended, Claims 1-4, 7, 10, 12-20, and 29-30 are drawn or contain subject matter drawn to the elected subject matter; Claims 5-6, 8-9, and 23-25 exclude using α_1-antitrypsin as the serine protease for treatment. Thus, Claims 5-6, 8-9, and 23-25 are withdrawn from further consideration as non-elected inventions, and Claims 1-4, 7, 10, 12-20, and 29-30 will be examined herein.

The Examiner notes that comments previously set forth against this claims concerning typographical errors and clarity were made in error since the subject matter of these claims has not been examined outside of the elected species, α_1-antitrypsin.

Priority

3. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/123,167 filed on March 5, 1999.

Information Disclosure Statement

4. As previously noted in Paper No. 9, the information disclosure statement filed on May 4, 2001 (Paper No. 3) has not been considered because the references were not filed for consideration. Applicants noted that the references have been filed in related cases; this is insufficient unless the related case is a parent application. For these references to be cited on the front page of any patent, copies of the documents must be filed with the instant application.

The IDS filed on June 19, 2000 (Paper No. 2) has been considered as previously noted.

Drawings

5. The drawings are considered informal for the reasons cited in PTO-948 attached to Paper No. 9. Appropriate correction is required in response to the instant Office action and may not be held in abeyance (see 37 C.F.R. § 1.85(a)).

Withdrawn - Objections to the Specification

6. Previous objection to the amendment filed May 14, 2002 (Paper No. 12) under 35 U.S.C. § 132 because it introduces new matter into the disclosure is withdrawn by virtue of Applicants' amendment and/or the Examiner's reconsideration. Concerning the phrase in Claim 16, "at least once daily", the Examiner agrees with Applicants' position that support is found on page 8.

New – Objection to the Specification

7. The amendment filed January 29, 2003 (Paper No. 15) is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material

which is not supported by the original disclosure is as follows: in non-elected Claim 9, the limitation of "at least 0.001 and **no greater than 7.0** g/kg body weight" (emphasis added) is considered new matter. The ranges of 0.001 to 7.0 and of 1 to 70 are supported in the specification on page 7, line 28. Thus, the amendment to Claim 4 with a range of 0.001 and no greater than 70 is supported by the combination of the two ranges. However, in Claim 9, the phrase "no greater than 7.0" is not verbatim supported in the specification, and the phrase is contradicted with the second range that goes as high as 70 g/kg. Thus, the phrase is considered new matter.

Applicant is required to delete and/or amend the phrase and/or cite clear support in the specification as originally filed to support the range claimed.

Withdrawn - Objections to the Claims

8. Previous objection to Claims 1-17 for having a duplicate member in the Markush group is withdrawn by virtue of Applicants' amendment.

New – Objections to the Claims

9. Claims 1-4, 7, 10, 12-20, and 29-30 are objected to for containing non-elected subject matter.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

10. Previous rejection of Claims 3, 4, and 22 under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms α1-antitrypsin-like agent, variant of α1-antitrypsin, anticathepsin

G agent, antitryptase TL2-agent, antifactor Xa agent, antielastase agent, and antiproteinase-3 agent is withdrawn by virtue of Applicant's amendment deleting these terms.

11. Previous rejection of Claim 18 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "exhibiting mammalian α1-antitrypsin or α1-antitrypsin-like activity" is withdrawn by virtue of Applicants' deleting the phrase.

New - Claim Rejections - 35 U.S.C. § 112, second paragraph

12. Claims 1-4, 7, 10, 12-20 and 29-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "wasting disease" is unclear as to its metes and bounds. On page 14 of the instant specification, the term wasting disease "includes" cancer, neurodegenerative diseases, myocardial infarction, and stroke. The term "includes" does not define the metes and bounds of the term "wasting disease". As such, the term is unclear as to what other diseases might be included. Additionally, the further limiting nature of Claim 29 indicates that more than just these three diseases are included. Again, leaving the skilled artisan to wonder what other diseases are "wasting diseases". Appropriate clarification is required.

13. Claims 3-4 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "and combinations thereof" is unclear following "an oxidation-resistant or free radical-resistance variant thereof". Can the combination be an oxidation-resistant variant and a free radical-resistance variant? It is unclear if these two species are one or

more than one. Moreover, the structure of these variants is unclear as a genus since only a single mutation is mentioned, position 358, as controlling this feature. Thus, the nature of these variants is unclear if it is limited to 358-mutants or not in view of the specification. Clarification is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

14. Previous rejection of Claims 4, 9, 12-14, 16, and 24 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicants' amendment.

15. Previous rejection of Claims 1-17 under 35 U.S.C. § 112, first paragraph, enablement, is withdrawn by virtue of the Examiner's reconsideration. The previous rejection was set forth in error against claims to methods of inhibiting apoptosis. Enabling methods of inhibiting apoptosis in subjects is a different issue than relying on a link between apoptosis and disease.

16. Previous rejection of Claim 18 under 35 U.S.C. § 112, first paragraph, enablement, is withdrawn by virtue of the Examiner's reconsideration in view of Applicants' amendment. The Examiner will comment on Applicants' arguments.

Applicants note the Wands factors and undue experimentation, both of which had been addressed in the Examiner's original rejection. Applicants argue from M.P.E.P. § 2164.01(c) concerning the enablement of a compound or composition claim; this argument is off point since the claims are drawn to methods of use. Applicants comment in their remarks that there is a "casual link between disease and apoptosis"; this is precisely the Examiner's point in the enablement rejection since a "casual link" does not enable the claimed methods without undue

experimentation. Applicants argue that, due to this link, "it is rational that an inhibitor or serine proteases ... can be used to treat these diseases without resort to undue experimentation". The Examiner fails to see how this is rational when the only experiments in "subjects" (rats) included rats that suffered from the induced MI or stroke despite treatment with α_1-antitrypsin.

Applicants summarize publications briefly discussed in the declaration under 37 U.S.C. § 1.132 by the inventor, Leland Shapiro. Hetts discusses apoptosis-linked genes as "**potentially** excellent targets for ...therapeutic intervention in disease processes" (emphasis added) and further notes that "for apoptosis-based therapy to be feasible, therapeutic molecules must be delivered to and active only in specific target cells: indiscriminate inhibition of apoptosis could lead to widespread hyperplasia" and "a further caveat is that saving a cell from death is not necessarily the same thing as preserving its function" which would be required for an effective treatment. None of these issues are addressed by the instant application and would require undue experimentation to solve for treatment of diseases using serine protease inhibitors. Virtually all of the examples of drugs for rheumatic diseases in Grodzicky *et al.* are apoptosis inducers having the opposite effect of the methods claimed herein. While Honig *et al.* link neurological diseases and cell death, a link between apoptotic cell death and said diseases is not described, nor are treatments of said diseases with apoptosis inhibitors. Mahidhara *et al.* link apoptosis and sepsis but also note that "manipulation of any one pathway down stream from the central stimulus can have a multitude of potential effects which are difficult to predict in the clinical situation if extrapolated even from well designed experimental models" and discuss no treatments based on this link. Articles by Sanders and James link apoptosis and cardiac disease but, again, offer no treatments based on this link. While Ueda *et al.* describe a definite link between apoptotic

pathways and acute renal failure, they also note that "it is still premature to seek therapeutic benefits based on our current knowledge of apoptosis in human diseases, including acute renal failure", and they describe no treatments using apoptosis inhibitors. Rust *et al.* describe only little information concerning a link between liver disease and apoptosis and offer no treatments in this vein.

Articles of Aprikyan *et al.* and Ancliff *et al.* describe a link between neutrophil elastase (NE) and neutropenia. It seems reasonable that a serine protease that inhibits NE would be an effective treatment; however, the link between this and apoptosis is unclear particularly since neutropenia is not mentioned in the specification. The Bogdan *et al.* article describes a link between TNF and meningitis via apoptosis, but no treatments are suggested. USPN 6489308 describes a link between serine protease inhibitors and nitric oxide which can link serine protease inhibitors to sepsis treatment; however, these inhibitors are not described as treatments for sepsis.

Beginning on paragraph 14 of the declaration, a new experiment is presented. Assays are described in paragraphs 15-18, then results are presented in paragraphs 19-21. The Examiner agrees that Figure 1 demonstrates the ability of AAT to reduce SU5416-induced apoptosis in rats; the Examiner notes that the "SuSim" column in Figure 1 and Table 1 is unclear. The Examiner agrees that Figures 2A and 2B show an inhibitory effect of AAT of SU5416-induced apoptosis. The Examiner agrees that Table 2 shows, via the TUNEL assay data, that AAT reduces SU5416-induced apoptosis. The Examiner does note that in the TUNEL assay, Su+AT does not return the apoptosis level to that of the control while in the MLI assay, the Su+AT sample showed lower-than-control levels of apoptosis. All these experiments are presented

along side the paper by Kasahara *et al.* in defense of serine proteases, particularly AAT, as inhibitors of apoptosis and thus as treatments for apoptosis-related diseases. However, Kasahara *et al.* uses all these experiments to identify, "in an animal model, ...that chronic blockade of VEGF receptors induces apoptosis" and not to identify a treatment via said animals for emphysema. In other words, Kasahara *et al.* was looking for an apoptotic factor in emphysema disease and found it in VEGF receptors. This is not the same thing as regulation of VEGF receptors inhibiting apoptosis and thus inhibiting emphysema. Kasahara *et al.* do not make such a bold assumption, in fact, they merely "suggest that inhibition of apoptosis may offer a new strategy for the treatment of emphysema" and offer no enablement to that end.

17. Previous rejection of Claims 19-20 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for *reducing* apoptosis in cell or tissue culture, does not reasonably provide enablement for *inhibiting* apoptosis in cell or tissue culture or even reducing apoptosis in a mammalian organ is withdrawn by virtue of Applicants' amendment to the claims.

New - Claim Rejections - 35 U.S.C. § 112, first paragraph

18. (New) Claim 14 is rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of "no greater than 200 μM" is considered new matter. The range of 10 pM to 2 mM is supported in the specification on page 7, line 16. Thus, the

amendment to Claim 12 is supported by the specification as originally filed. However, in Claim 14, the phrase "no greater than 200 μM" is not verbatim supported in the specification, and the phrase is contradicted with the largest range that goes as high as 2 mM. Thus, the phrase is considered new matter. Applicants must delete and/or amend the phrase and/or cite clear support in the specification as originally filed to support the range claimed.

19. Claims 3-4 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 3 and 25 utilize, as an option, an oxidation-resistant or free radical-resistant variant of α_1-antitrypsin wherein the use of this serine protease inhibitor is claimed solely by function and without any structural limitations.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical

characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a species of an oxidation-resistant variant of α_1-antitrypsin is described as a Met^{358} variant. The mechanism of oxidation resistance is hypothesized to be due to stability of the variant to the neutrophil oxidative burst. No other mechanisms of imparting oxidation-resistance or free radical-resistance in α_1-antitrypsin is described. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. Therefore, claims drawn to methods of using variants that are only functional described with a single structure example are not adequately described.

20. Claims 3-4 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being possibly enabling for methods using known oxidation-resistant or free radical-resistant α_1-antitrypsin variants, does not reasonably provide enablement for methods using unknown oxidation-resistant or free radical-resistant α_1-antitrypsin variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. To practice the claimed methods effectively to the extent they are claimed (i.e., their entire scope) would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant specification, a species of an oxidation-resistant variant of α_1-antitrypsin is described as a Met^{358} variant. The mechanism of oxidation resistance is hypothesized to be due to stability of the variant to the neutrophil oxidative burst. No other mechanisms of imparting oxidation-resistance or free radical-resistance in α_1-antitrypsin is described. The art identifies no other oxidation-resistant variant of α_1-antitrypsin. Moreover, it is wholly unpredictability whether or not another oxidation-resistant variant of α_1-antitrypsin could be identified, even with copious amounts of experimentation, none of which is guided by the instant specification. Thus, the instant claims are not enabled to the full extent of their scope.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

21. Previous rejection of Claims 21-22 under 35 U.S.C. § 102(b) as being anticipated by van Molle *et al.* is withdrawn by virtue of Applicants' cancellation of said claims.

New - Claim Rejections - 35 U.S.C. § 102

22. Claims 1-4 and 30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Van Molle *et al.* (see PTO-892 with Paper No. 9). The instant claims are drawn to methods of treatment between 0.001 and 70 g/kg body weight in a subject suffering from toxin-induced liver injury using α_1-antitrypsin wherein said method includes a measurement of a decrease in apoptosis.

Van Molle *et al.* teach treatment of mice with liver toxicity induced by TNF (tumor necrosis factor) plus GalN (galactosamine) using 0.5 mg of α_1-antitrypsin per mouse (see page 3556, right column). Provided the mouse weighs between 0.0071 grams and 500 grams (a likely inherent feature of the experiment), this dose is within the claimed range. Van Molle *et al.* monitor the treated mice for apoptosis as measured by the degree of DNA fragmentation in blood samples (see page 3557, Figure 1).

23. Claims 1, 3, 4, 10, 15, and 30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Emerson *et al.* (USPN 4,829,054). The instant claims are drawn to methods of treatment between 0.001 and 70 g/kg body weight in a human subject suffering from sepsis using α_1-antitrypsin intravenously. While the preamble notes a "method of inhibiting apoptosis", this is an inherent feature of a dose of α_1-antitrypsin within the prescribed range.

Emerson *et al.* teach treatment of humans with ARDS for cases of impending sepsis with α_1-antitrypsin (see column 1, lines 20-33 and 60-63). Treatment includes dosing intravenously at 0.1 g/kg (or100 mg/kg) as demonstrated in the experimental protocol using sheep as a mammalian model (see column 4, line 12 and line 20).

24. Claims 1, 3, 4, 10, 12-16, and 30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Lezdey *et al.* (USPN 5,532,215). The instant claims are drawn to methods of treatment between 0.001 and 70 g/kg body weight in a human subject suffering from HIV using α_1-antitrypsin by daily injection wherein the drug concentration in the blood is maintained at between 0.5 μM and 200 μM (between 0.1 and 40 mg/kg – conversion of 50 μM=10 mg/kg from the specification on page 16). While the preamble notes a "method of inhibiting apoptosis", this is an inherent feature of a dose of a serine protease inhibitor within the prescribed range.

Lezdey *et al.* teach methods of treating viruses in human, particularly HIV infection, with α_1-antitrypsin (see Abstract and column 6, lines 25-31) in daily doses of about 0.06 to 1.2 mg/kg body weight using infusible compositions to maintain a high blood concentration (see column 6, lines 45-57).

25. Claim 18 is rejected under 35 U.S.C. § 102(b) as being anticipated by Emerson *et al.* (USPN 4,829,054) as evidenced by Mahidhara *et al.* (Apoptosis and sepsis. Crit. Care Med. (2000) 28:4 (Suppl.)). The instant claims are drawn to methods of prophylactically treating an individual at risk for a pathological condition that is precipitated by apoptosis with at least one serine protease inhibitor (α_1-antitrypsin).

Emerson *et al.* teach that "[i]n cases of impending sepsis and shock, prophylactic administration of AT-III and alpha-1-PI should be beneficial" (see column 1, lines 60-62); AT-III is antithrombin III, a serine protease inhibitor, and alpha-1-PI is α_1-proteinase inhibitor (a.k.a. α_1-antitrypsin as per Registry Number 9041-92-3). Sepsis is linked to apoptosis as evidenced by Mahidhara *et al.*

26. Claims 19-20 are rejected under 35 U.S.C. § 102(a) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Van Molle *et al.* The instant claims are drawn to a method of reducing apoptosis in mammalian cell culture using α_1-antitrypsin.

Van Molle *et al.* teach as described as above. Additionally, Van Molle *et al.* teach treatment of mammalian HepG2 cell lines with 0.25 mg/ml α_1-antitrypsin (5 μM) (see page 3561, right column and page 3563, Figure 4). While Van Molle *et al.* report no detected inhibition of apoptosis, this administration of α_1-antitrypsin, at this concentration, is squarely within Applicants' proposed administration range for effect. Thus, if the specification has enabled the instant method wherein apoptosis is inhibited at this concentration of α_1-antitrypsin, Van Molle *et al.* have certainly practiced the invention.

However, if Applicants were to contend that the lack of noticeable inhibition of apoptosis on the part of Van Molle *et al.* indicates that the concentration of α_1-antitrypsin was not an effective concentration, the Examiner would reply that it would have been obvious to increase the concentration of α_1-antitrypsin in the cell culture experiment so that apoptotic inhibitory results would have been seen since these results were found *in vivo* as reported by Van Molle *et al.* One would have been motivated to practice this version of the invention because the

assessment of the effects of α_1-antitrypsin is more facile in cell culture rather than in whole animals.

Summary of Pending Issues

27. The following is a summary of the issues pending in the instant application:

a) Claims 5-6, 8-9, and 23-25 stand withdrawn from further consideration as non-elected inventions.
b) The information disclosure statement filed on May 4, 2001 (Paper No. 3) has not been considered.
c) The drawings are informal.
d) The amendment filed January 29, 2003 (Paper No. 15) is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure.
e) Claims 1-4, 7, 10, 12-20, and 29-30 stand objected to for containing non-elected subject matter.
f) Claims 1-4, 7, 10, 12-20 and 29-30 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "wasting disease".
g) Claims 3-4 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "and combinations thereof" and for the nature of these variants.
h) Claim 14 stands rejected under 35 U.S.C. § 112, first paragraph, new matter.
i) Claims 3-4 stand rejected under 35 U.S.C. § 112, first paragraph, written description.
j) Claims 3-4 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.
k) Claims 1-4 and 30 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Van Molle *et al.* (see PTO-892 with Paper No. 9).
l) Claims 1, 3, 4, 10, 15, and 30 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Emerson *et al.* (USPN 4,829,054).
m) Claims 1, 3, 4, 10, 12-16, and 30 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Lezdey *et al.* '215 (USPN 5,532,215).
n) Claim 18 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Emerson *et al.* (USPN 4,829,054) as evidenced by Mahidhara *et al.* (Apoptosis and sepsis. Crit. Care Med. (2000) 28:4 (Suppl.).
o) Claims 19-20 stand rejected under 35 U.S.C. § 102(a) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Van Molle *et al.*

Conclusion

28. Claims 1-4, 7, 10, 12-20, and 29-30 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
September 19, 2003